Catecholamine Function in Posttraumatic Stress Disorder

Emerging Concepts

Edited by
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PROGRESS IN PSYCHIATRY

Note: The authors have worked to ensure that all information in this book concerning drug dosages, schedules, and routes of administration is accurate as of the time of publication and consistent with standards set by the U.S. Food and Drug Administration and the general medical community. As medical research and practice advance, however, therapeutic standards may change. For this reason and because human and mechanical errors sometimes occur, we recommend that readers follow the advice of a physician who is directly involved in their care or in the care of a member of their family.

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Chapter 9

Stress-Induced Alterations in Plasma Catecholamines and Sympathetic Nervous System Function in PTSD

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Some investigators (Keane et al. 1985; Kolb 1987; see also McFall and Murburg, Chapter 7, this volume, for review) have hypothesized that the increased physiological reactivity to trauma-relevant stimuli seen in posttraumatic stress disorder (PTSD) is due to conditioned activation of the sympathetic nervous system (SNS). According to this model, unconditioned emotional, behavioral, and physiological responses to life-threatening situations become conditioned to otherwise neutral internal and external stimuli so that these conditioned stimuli come to elicit elements of the original "fight-flight" response, including increased SNS activation. To date, a number of studies have

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tested this hypothesis in combat veterans with PTSD using paradigms in which autonomic responses to combat-related stimuli were measured (see McFall and Murburg, Chapter 7, for review). These studies have generally found that PTSD patients displayed greater increases in heart rate and blood pressure than did normal or psychiatric control groups in response to trauma-relevant stimuli (Blanchard et al. 1982, 1986; Malloy et al. 1983; Pitman et al. 1987). Time-dependent sensitization has been proposed as an alternative explanation for this autonomic hyperresponsiveness. According to this model, stress exposure causes biological changes that result in sensitization of autonomic and behavioral responses to subsequent exposure to related stimuli (see Antelman and Yehuda, Chapter 4; Charney et al., Chapter 6; Rausch et al., Chapter 14, this volume).

Neuroendocrine studies investigating peripheral catecholamine function in traumatized populations and PTSD patients have reported increased heart rate, blood pressure, and urinary norepinephrine and epinephrine levels, and reduced number of platelet alpha$_2$ (α_2)–adrenergic binding sites in these subjects compared with control subjects (Davidson and Baum 1986; Kosten et al. 1987; Perry et al. 1988). Although suggesting that net SNS activity may be increased following trauma, these studies have not been designed to discriminate tonic changes in SNS activity from phasic changes that might occur in response to trauma-related stimuli. In the current study we measured changes in emotional state, heart rate, blood pressure, and plasma catecholamine levels in response to combat-related and combat-unrelated stressors in combat veterans with PTSD and in control subjects. We hypothesized that combat veterans with PTSD would show greater physiological and emotional responses to the combat-related stressor, but not to the combat-unrelated stressor, than would control subjects.

METHODS

Subjects

Ten Vietnam veterans with PTSD and 14 control subjects participated. All subjects were males who were free from diagnosabl medical illness. The subjects had abstained from alcohol and all drugs for at least 2 weeks prior to participation and for at least 4 weeks prior to study had not taken psychotropic drugs or medications that are known to alter plasma catecholamine levels. All subjects abstained from caffeine, nicotine, and nourishment (except for ad libitum water) for 12 hours before the procedure began.

The PTSD patients were combat veterans who met DSM-III-R criteria (American Psychiatric Association 1987) for PTSD by the Structured Clinical Interview for DSM-III-R (SCID; Spitzer et al. 1987). These patients exceeded published cutoff scores on tests (see Table 9–1) that had previously been found to identify high levels of combat exposure and PTSD in a large percentage of veterans (Keane et al. 1988; Laufer et al. 1981; Zilberg et al. 1982). Other Axis I disorders in this group were diagnosed based on the patient version of the SCID (SCID-P; Spitzer et al. 1987). Comorbid diagnoses included major depression (40%); major depression in partial remission (30%); dysthymia (30%); bipolar disorder, depressed (10%); generalized anxiety disorder (20%);

Table 9–1. Characteristics of subjects

	PTSD	Control
n	10	14
Mean age	40.5	39.6
Mean % of ideal body weight	117	111
Length of combat (months)	11.4	4.7[a]
Mean CES	12	7.7[a]
Mean SCID PTSD score	11	3.6[a]
Mean MSCR PTSD score	121.3	69[a]
Mean IES score		
Intrusion subscale	25	10[a]
Avoidance subscale	23.8	12[a]
Current comorbidity (mean number of diagnoses/person)	1.8	0.2

Note. CES = Combat Exposure Scale; SCID = Structured Clinical Interview for DSM-III-R; IES = Impact of Event Scale; MSCR = Mississippi Scale for Combat, Revised.

[a]Values given are for the three Vietnam combat veterans in this sample.

obsessive-compulsive disorder (10%); social phobia (20%); and adjustment disorder (10%). Nine subjects had a history of substance use disorder that had been in remission for at least 2 weeks prior to the study. The literature to date indicates that presence of psychiatric conditions other than PTSD does not influence psychophysiological response to combat-related laboratory stressors (McFall et al. 1989; see also McFall and Murburg, Chapter 7, this volume).

Control subjects were two Vietnam combat veterans with psychiatric disorders other than PTSD, one asymptomatic Vietnam combat veteran without PTSD, four military veterans without combat exposure (three of whom were free from psychiatric disorder and one of whom had a mild simple phobia), and seven nonveterans without mental disorder.

Stimulus Materials

The experimental stressors consisted of two 10-minute narrated videotapes depicting combat-unrelated and combat-related situations, respectively. The combat-unrelated stressor film showed the aftermath of serious automobile accidents, while the combat stressor film consisted of combat footage taken during the Vietnam War. In a previous study using similar techniques (Malloy et al. 1983), the majority of subjects with PTSD became so upset when viewing war-related films that they were unable to complete the experiment. Therefore, to ensure that subjects would view both films, and to prevent possible carry-over effects from the combat film to the automobile film, the latter was administered before the combat film in every case in the present study.

Procedure

Subjects were admitted individually to the Special Studies Unit at the Seattle VA Medical Center at noon. Participants remained in a supine position throughout the study. An intravenous (iv) catheter was inserted in the dorsum of the hand or wrist to permit repeated nontraumatic blood sampling. The catheterized hand was then placed in a warming box at 60°C to arterialize the venous blood. Subjects rested for 30 minutes after the iv catheter was properly operating, and then baseline blood samples, mood state assessments (affect ratings), and vital sign measurements were performed every 10 minutes for 30 minutes.

The automobile accident film was then shown to subjects. Vital signs were measured five times, at 2-minute intervals, during viewing, and blood samples were drawn 5 and 10 minutes after the film began. Affect ratings were completed immediately after the film ended. The film was followed by a 30-minute recovery period, during which five measurements of vital signs were made at 2-minute intervals followed by two more measurements at 10-minute intervals. Blood samples were drawn 5, 10, 20, and 30 minutes after the film ended. Affect ratings were obtained again at the end of the recovery period. Subjects rested for another 30 minutes and then had vital signs and affect ratings measured and blood drawn to determine whether the variables had returned to baseline levels. The sequence of assessments for each variable during the combat film and subsequent recovery phase was identical to that described for the automobile film and recovery period. Thirty minutes after the combat film recovery phase had elapsed, final measurements of vital signs and affect ratings were made, and blood samples were obtained.

Dependent Measures

Affect ratings consisted of assessments of subjects' mood state that were made using self-ratings of 17 descriptive adjectives on a 5-point scale indicating the extent to which subjects experienced each affect "now." A total score (possible range 0–68) was calculated for the 17 adjectives at each time point. Blood pressure and heart rate were measured using an automated ultrasonic detector (Dinamap, Critikon, Tampa, Florida).

Circulating levels of norepinephrine and epinephrine were measured in arterialized forearm venous plasma, as described in Murburg et al., Chapter 8, this volume.

RESULTS

Data were consolidated to establish a single score for each variable during each of the following assessment intervals: baseline, automobile stress film, automobile film recovery, precombat film rest, combat film, combat film recovery, and end. Subjects' consolidated scores for a particular period represented an average of the individual measurements made during that period, with the exception of the precombat film rest and end periods, during which only one measurement was made. The means (± SEM) for dependent measures during each assessment period are presented in Table 9–2.

Comparisons Between PTSD and Control Subjects

Mann-Whitney tests were performed to evaluate the statistical significance of comparisons between PTSD and control subjects. One-tailed probability values were used to test hypothesized directional contrasts, and two-tailed values were applied to comparisons for which no directional hypotheses were formulated. Difference from baseline score was calculated for all dependent variables, and between-group comparisons were made for each experimental period.

During the automobile film, PTSD subjects reported significantly greater subjective emotional arousal than did contro subjects ($Z = -2.26$, $P < 0.03$). However, this greater affective arousal in PTSD subjects compared with control subjects was no accompanied by significant elevations in vital signs or in plasma catecholamines. During the recovery period following the automobile film, PTSD patients did not differ significantly from control subjects.

During the pre–combat film rest interval, PTSD subjects ha higher heart rates than did control subjects ($Z = -2.17$; P <0.0 but did not differ significantly from control subjects on any othe measure. The combat film evoked significantly greater heart ra ($Z = -2.87$, $P < 0.002$), diastolic blood pressure ($Z = -2.58$, P 0.005), affect raftings ($Z = -3.25$, $P < 0.006$), and plasma epinep rine ($Z = -1.76$, $P < 0.04$), but not systolic blood pressure plasma norepinephrine responses, in PTSD subjects than in co trol subjects.

During the post–combat film recovery period, PTSD patien continued to show elevated affect ratings ($Z = -2.73$, $P < 0.00$ heart rate ($Z = -1.70$, $P < 0.04$), systolic blood pressure ($Z = -2.1$

Table 9–2. Results: affect ratings, vital signs, and plasma catecholamines

Experimental period	AR	HR	SBP	DBP	NE	EPI
PTSD subjects						
Baseline	12.1 ± 3.1	63.2 ± 2.2	124.0 ± 3.6	78.5 ± 2.6	244.0 ± 15.5	70.4 ± 10.2
Automobile film (Δ)[a]	10.2 ± 2.1	1.6 ± 1.0	2.7 ± 1.4	1.4 ± 0.6	−11.0 ± 14.6	3.1 ± 5. 2
Automobile recovery (Δ)	−2.5 ± 2.3	1.4 ± 0.9	1.3 ± 2.4	0.9 ± 0.9	−12.2 ± 14.3	8.2 ± 6.7
Rest (Δ)	−1.7 ± 1.6	3.0 ± 1.8	0.8 ± 2.4	−0.8 ± 1.5	3.0 ± 14.1	5.6 ± 7.3
Combat film (Δ)	23.7 ± 3.7	6.8 ± 1.8	5.9 ± 2.6	4.1 ± 1.1	11.5 ± 17.4	15.1 ± 7.1
Combat recovery (Δ)	11.4 ± 3.7	4.5 ± 1.2	6.7 ± 2.2	4.5 ± 1.5	0.3 ± 14.6	24.6 ± 4.2
End/Rest (Δ)	8.5 ± 5.1	5.9 ± 2.2	2.9 ± 2.6	2.6 ± 1.9	−0.9 ± 2.1	35.1 ± 13.8
Control subjects						
Baseline	4.8 ± 1.0	63.0 ± 3.0	121.5 ± 2.8	7.5 ± 1.9	229.7 ± 21.4	76.5 ± 9.7
Automobile film (Δ)	4.4 ± 1.5	1.2 ± 1.1	2.2 ± 2.1	0.3 ± 1.4	14.6 ± 118	4.5 ± 5.5
Automobile recovery (Δ)	−1.2 ± 0.5	0.7 ± 0.7	0.8 ± 1.7	−0.4 ± 1.4	−6.7 ± 9.0	0.6 ± 6.6
Rest (Δ)	−1.1 ± 0.4	−1.4 ± 1.0	4.2 ± 2.3	1.0 ± 1.8	1.0 ± 10.1	−2.2 ± 8.5
Combat film (Δ)	6.2 ± 1.4	0.6 ± 1.1	2.6 ± 2.2	0.6 ± 1.3	−10.4 ± 9.0	−8.3 ± 7.8
Combat recovery (Δ)	0.3 ± 0.6	2.3 ± 1.2	0.9 ± 2.1	0.6 ± 1.5	−3.8 ± 10.8	−6.1 ± 7.4
End/Rest (Δ)	0.6 ± 1.0	1.1 ± 1.1	5.3 ± 2.6	1.9 ± 1.6	−6.5 ± 17.8	5.5 ± 9.7

Note. AR = affect ratings; DBP = diastolic blood pressure (mmHg); EPI = plasma epinephrine (pg/ml); HR = heart rate (beats per minute); NE = plasma norepinephrine (pg/ml); SBP = systolic blood pressure (mmHg).
[a]Δ indicates change from baseline level.

$P < .016$), diastolic blood pressure ($Z = -2.58$, $P < .005$), and plasma epinephrine ($Z = -3.02$, $P < 0.0125$), but not plasma norepinephrine. One hour after the combat film had ended, PTSD subjects continued to show significantly greater increases in heart rate than did control subjects ($Z = -2.17$, $P < 0.03$), but were comparable to control subjects on all other measures.

Comparisons Within Subject Groups

Wilcoxon signed rank tests were performed to evaluate statistical significance of comparisons between experimental conditions for each subject group. These comparisons determined whether subjects within each group responded differentially to the two experimental stressors.

PTSD subjects. For PTSD subjects, viewing the automobile film was accompanied by an increase only in systolic blood pressure ($Z = 1.78$, $P < 0.05$), diastolic blood pressure ($Z = -1.78$, $P < 0.05$), and affect ratings ($Z = -2.80$, $P < 0.01$) compared with baseline. The recovery phase following the automobile film was not associated with significant changes in any measurement relative to baseline.

The combat film evoked significant increases in heart rate ($Z = 2.80$, $P < 0.01$), systolic blood pressure ($Z = 1.89$, $P < 0.05$), diastolic blood pressure ($Z = 2.45$, $P < 0.01$), epinephrine ($Z = 2.19$, $P < 0.05$), and affect ratings ($Z = -2.80$, $P < 0.01$). During the recovery phase following the combat film, PTSD subjects continued to exhibit increased affect ratings ($Z = -2.42$, $P < 0.01$), heart rate ($Z = -2.50$, $P < 0.01$), systolic blood pressure ($Z = 2.19$, $P < 0.05$), diastolic blood pressure ($Z = 2.34$, $P < 0.01$), and plasma epinephrine ($Z = 2.70$, $P < 0.01$). At the final assessment, PTSD subjects continued to have increased heart rate ($Z = -2.31$ $P < 0.01$) and plasma epinephrine ($Z = -2.37$, $P < 0.01$) compared with baseline. PTSD subjects reacted more strongly to the combat film than to the auto film, with significantly higher affect ratings ($Z = 2.67$, $P < 0.01$), heart rate ($Z = 2.80$, $P < 0.01$), and diastolic blood pressure ($Z = -1.84$, $P < 0.05$). Plasma epinephrine was also higher in PTSD subjects during the combat film than during the automobile film, but this difference did not quite achieve signifi cance ($Z = 1.60$, $P < .05$). Similarly, the group showed significantly greater elevations in affect ratings ($Z = 2.80$, $P < 0.01$), heart rate ($Z = 2.24$, $P < 0.05$), systolic blood pressure ($Z = -1.99$, $P < 0.05$), diastolic blood pressure ($Z = 1.88$, $P < 0.05$), and plasma epinephrine ($Z = 1.89$, $P < 0.05$) during the combat film recovery interval than during the automobile film recovery interval.

Control subjects. Control subjects exhibited increased affect ratings relative to baseline ($Z = -2.27$, $P < .01$), but exhibited no increases in measures of physiological arousal in response to the automobile accident film. During the recovery period following the automobile film, control subjects actually had lower affect rating scores than at baseline ($Z = -2.09$, $P < 0.04$). The combat film evoked a significant increase only in affect ratings ($Z = -3.18$, $P < 0.002$) in control subjects. No significant differences between baseline and either the post–combat film recovery period or the end of study assessment were found for any variable. Comparisons between control subjects' responses to the automobile film versus the combat film and to the automobile recovery period versus the combat recovery period showed only a significantly greater epinephrine response to the automobile film ($Z = -2.04$, $P < 0.02$).

DISCUSSION

The results of this study indicate that exposure to combat-related laboratory stimuli is associated with increased emotional distress and autonomic activation in Vietnam combat veterans with PTSD. This autonomic activation is manifested by increased arterialized plasma levels of epinephrine, as well as by elevated heart rate, systolic blood pressure, and diastolic blood pressure. The pattern of emotional and autonomic responses exhibited by veterans with PTSD differed from that of control subjects, who showed minimal changes in autonomic functioning during exposure to combat-related stimuli. Moreover, the increases in plasma epinephrine and other indices of SNS activity in PTSD subjects were more pronounced in response to the combat-related stressor than to the combat-unrelated stressor, whereas control subjects showed a greater epinephrine response to the automobile film. These findings are consistent with previous psychophysiological studies in which PTSD subjects have been found to exhibit relatively greater autonomic responsiveness to trauma-specific cues (McFall et al. 1989; see also McFall and Murburg, Chapter 7, this volume), and lend support to the hypothesis that conditioning and sensitization may play roles in the pathophysiology of PTSD.

These findings are also quite interesting in light of the discussion by Aston-Jones et al. (Chapter 2, this volume) of locus coeruleus (LC) responses to meaningful cues in nonhuman primates. The combat film would of course be expected to be more "meaningful" than the auto accident film to combat veterans with PTSD, whereas for control subjects the automobile film would have represented a more directly meaningful stressful situation. Because greater increases in plasma epinephrine occurred in response to the combat film in PTSD patients and in response to the automobile film in control subjects, it is possible that sympathoadrenal as well as LC activation occurs selectively in response to psychologically or physiologically meaningful stressors in humans. The lack of an increase in control subjects' plasma epinephrine levels in response to the combat film (which caused a level of emotional distress simliar to that caused by the automobile film) suggests that the increase in plasma epinephrine in response to stressor exposure is not due solely to affective arousal.

In this study, measurements of autonomic activity in PTSD subjects remained elevated and in fact reached their highest levels during the recovery period following the combat film. Several subjects spontaneously reported that viewing the combat film activated distressing war-related memories that persisted into the recovery period. These memories may have served as repeated stressors, which in turn would have continued to activate the sympathoadrenal system. Consistent with this possibility, other investigators (Horowitz et al. 1973) have documented increased emotional distress and preoccupation with intrusive thoughts subsequent to exposure to films with stressful content. It is also possible, however, that mechanisms which normally terminate sympathoadrenal response to stressors may be impaired in PTSD patients.

In this study, plasma epinephrine, but not norepinephrine, levels increased in response to meaningful stressor stimuli. Plasma epinephrine derives primarily from the adrenal medulla, whereas norepinephrine is released from postganglionic sympathetic nerves. It has been suggested by a number of investigators that the sympathetic neural and adrenomedullary components of the SNS may be differentially activated, depending on the causal stimulus (Folkow 1984; Goldstein et al. 1987; Halter et al. 1984; Hjemdahl et al. 1984; Robertson et al. 1979; Ward et al. 1983). Thus, the combat-related stressors may have provoked a greater adrenomedullary than sympathoneural response in our PTSD group. This possibility is consistent with a growing body of evidence indicating that the SNS is capable of differential, rather than all-or-none, activation (Villacres et al. 1987).

It is important to emphasize that the interpretation of stress-induced plasma catecholamine responses requires careful attention to several physiological determinants. In a number of studies, certain psychological stressors such as the Stroop test have been found to cause greater increases in venous plasma levels of epinephrine than of norepinephrine (Robertson et al. 1979; Ward et al. 1983). However, norepinephrine levels in venous plasma are largely influenced by regional tissue factors (Goldstein et al. 1987; Hjemdahl et al. 1984). Because the outflow of sympathetic muscle nerves may decrease during some kinds of mental stress (Delius et al. 1972), with consequent decreased vascular resistance and increased blood flow and norepinephrine clearance through the muscle (Goldstein et al. 1987; Hjemdahl et al. 1984), the muscles become a site of net norepinephrine removal under such conditions. Thus, venous plasma levels of norepinephrine would be lower than those found in arterial or mixed venous samples (Hjemdahl et al. 1984).

In comparing the accuracy of arterial and venous plasma norepinephrine levels with norepinephrine release rates obtained by a radioisotope dilution technique, Goldstein et al. (1987) determined that the radioisotope dilution technique was the most sensitive in detecting SNS activation. Because SNS activation is accompanied by increased cardiac output and therefore increased total body norepinephrine clearance, arterial plasma norepinephrine levels in Goldstein et al.'s study were a less sensitive indicator of SNS activation than was the norepinephrine release rate. Again, because of the regional tissue effects on plasma norepinephrine values, venous plasma norepinephrine was not a good indicator of SNS activity.

Norepinephrine measured (as in this present study) in arterialized plasma reflects sympathetic activity more accurately than norepinephrine measured in venous plasma, but less accurately than in the kinetic studies described by Goldstein et al. (1987) and others (Best and Halter 1982; Esler 1982; Veith et al. 1986). Thus, we cannot rule out the possibility that the lack of change in arterialized plasma levels of norepinephrine in this study resulted from our failure to detect a small increase in norepinephrine release that may have been obscured by a simultaneous increase in total body norepinephrine clearance. Similarly, we cannot exclude the possibility that decreased clearance of epinephrine from plasma accounts for some or all of the elevation of epinephrine levels observed here. Moreover, regional increases in sympathetic outflow to specific organs such as the heart may have occurred in response to trauma-related stimuli, but may have been obscured by factors such as the relatively small contribution by the cardiac branch of the SNS to circulating plasma norepinephrine, and possibly by simultaneous decreases in sympathetic outflow to other organs. More sophisticated (and invasive) sampling methods would be needed to investigate regional differences in SNS responses to trauma-related stimuli.

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